DETAILED ACTION

Claims 1, 6, 7, 10-19 are pending and are considered on the merits. Applicants' species election of 6-hydroxy-2,5,7,8,-tetramethylchroman 2-carboxylic acid is acknowledged and still in effect.

Claim Rejections - 35 USC § 112

INDEFINITE

Claims 1, 6, 7, 10-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 now recites "at most 0.5% by weight" and "1 to 10% by weight". These recitations are indefinite because the denominator of the ratio is not defined. For example, is the % by weight calculated from the weight of the solvents alone or by the total weight of the reaction mixture which includes the substrate and enzyme.

Claims 1, 6, 7, 10, 12-14, 16, 17 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, see MPEP § 2172.01. The omitted steps are: recovery or separation of the optically active chromancarboxylate from the optically active chromancarboxylic acid.

The claims are incomplete in the absence of a recovery/separation step for the product produced.

It is clear from the record and would be expected from conventional preparation processes that the ester must be isolated from the acid. Thus, the claims fail to claim the 'Complete" process since the recovery/separation step is missing from the claims. The metes and bounds of the claimed process are therefore not clearly established or delineated.

Claim Rejections - 35 USC § 103

Claims 1, 6, 7, 10-14, 17-19 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over JP 2003-144190 [N] in combination with Kirchner *et al.* [U].

The claims are directed to an enantiomeric esterification with an alcohol at 1-10% by weight in an organic solvent with a water content of at most 0.5% by weight of the compound of formula (1), elected species of 6-hydroxy-2,5,7,8-tetramethyl chromancarboxylic acid using an immobilized lipase from the genus *Candida*.

JP 2003-144190 describes an enantiomeric separation of the stereoisomers of (R,S) 6-hydroxy-2,5,7,8-tetramethyl chroman-2-carboxylic acid esters by stereoselectively hydrolyzing the S-ester using **immobilized *Candida*** *antarctica* lipase. Particularly preferred are alkyl esters with 1-4 carbons. The reference lacks the use of the reverse reaction, esterification to separate enantiomers of the compound.

Kirchner *et al.* disclose that enantiomers may be separated by hydrolysis or **esterification in organic solvents**. The advantages of the use of the esterification reaction instead of the hydrolysis reaction are (i) there is no need to convert an alcohol or an acid to an ester prior to the enzymatic resolution, thereby eliminating one synthetic step; (ii) stability of enzymes is much greater in organic solvents than in water, etc. page 7075, second column. Also, the process in Scheme I, table 1 uses 11 **mls of alcohol in 400 mls of hexane**, which is within the range of the claims. Also, **0.1% water** is added which is less than 0.5% as stated in the claims.

Thus, the reversal of the enantiomeric scheme from the stereoselective hydrolysis of a racemic acid ester employed in JP 2003-144190 to an enantioselective esterification of the racemic acid as described in Kirchner *et al.* for the advantages described would have been obvious.

With regard to claims 12, 19 one of skill in the art can hydrolyze the ester group from the enantiomerically purified acid ester if desired by simple base treatment, especially since there is no recovery of any specific optical product (R or S) and there are no further steps which require the use of the hydrolyzed acid. This does not appear to be a critical element, and hydrolysis of esters is well known in the art of organic chemistry.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 2003-144190 [N] in combination with Kirchner *et al.* [U] as applied to claims 1, 6, 7, 10, 11, 12-14, 17-19 above, and further in view of WO 91/15469 [N].

The claim is further drawn to separating the enantiomeric ester and acid by sodium carbonate extraction.

WO 91/15469 teach the separation of a resulting acid, ester enantiomers of an enzymatic resolution by aqueous base extraction (page 2, l. 22). Sodium carbonate is a weak base in water.

Therefore it would have been obvious to separate the enantiomeric ester and acid by sodium carbonate (base) aqueous extraction.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 2003-144190 [N] in combination with Kirchner *et al.* [U] as applied to claims 1, 6, 7, 10, 11, 12-14, 18, 19 above, and further in view of Pepin *et al.* [U2] and Gubicza *et al.* [V2].

The claim is further drawn to the removal of water during the reaction so that the water content of ? is at most 0.5% by weight of ?. The items in question have been deemed to be indefinite in the above 112, 2nd rejection.

Pepin *et al.* teach that low water activity is best when using an immobilized lipase from *Candida* (Novozyme 435) to enantioselectively catalyze an esterification reaction.

Gubicza *et al.* teach methods for water removal during asymmetric esterification in organic media, such as molecular sieves, salt hydrates, pervaporation, heteroazeotropic distillation (p. 687). Also, for an esterification reaction with *Candida cylindracea*, a 0.2-0.3% water content gave the best ester yield.

Therefore, it would have been obvious to remove water in the reaction of JP-2003-144190 as modified by Kirchner *et al.*, to maintain a water concentration of less than 0.5% when taken with Pepin *et al.* and Gubicza *et al.* because Pepin *et al.* teach the use of a low water concentration during *Candida* lipase enantioselective esterification reactions to improve yields and Gubicza *et al.* teach various methods of removing water in enantiomeric *Candida* esterification reactions.

One of ordinary skill in the art would have been motivated at the time of invention to make this substitution in order to obtain the resulting compound as suggested by the references with a reasonable expectation of success. The claimed subject matter fails to patentably distinguish over the state of the art as represented by the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

Response to Arguments

Applicant's arguments filed 12/29/08 have been fully considered but they are not persuasive.

Applicants argue that the claimed method is not incomplete because it is directed to producing an optically active chromancarboxylate. The inclusion of a recovery/separation step is directed to the complete process as disclosed in the specification and also insures that the claimed process has utility as there is no disclosed utility for such a mixture.

Applicants argue that the references do not suggest esterifying racemic chromancarboxylic acid in an organic solvent with an alcohol at a concentration

of 1-10% by weight using an immobilized lipase from *Candida* etc. The examiner contends that each and every limitation of claim 1 is taught by the references, please refere to the statement of the content of the references above. The applicants do not point out specific deficiencies, but merely state that the references do not teach all of the limitations of amended claim 1. Also, applicants argue that the enzyme can be used repeatedly, although this limitation does not appear in the claimed method. Even if it did appear, recycling of an immobilized lipase can be demonstrated to be routine in the art.

Applicants appear to argue unexpected results, but the claims are not commensurate in scope with the showing. Applicants argue that Kirchner *et al.* teach that there is no need to immobilize the enzymes since they are insoluble in organic solvents; however, one of skill in the art may use an immobilized enzyme in the absence of evidence to the contrary and the use of an immobilized enzyme is taught in JP 2003-144190. Applicant argue an increase in yield while using an immobilized enzyme, versus using a non-immobilized enzyme. While the yield appears to be lower while using Chirazyme L-2 versus Chirazyme L-2, carrier-fixed C2, the optical purity was higher when the non-immobilized Chirazyme was employed. Thus, unexpected results depend on what parameter is chosen and more importantly, must be limited to the conditions which yield the unexpected results. For example, different lipases have different water activity profiles (Wehtje *et al.* [W2]), but the claims are open to the use different lipases from different species of *Candida.* Also, the examples do not disclose what the concentration of water was in the reaction mixture or if any water at all is included in the reaction mixture which also has an effect on yield. Further, Petkar *et al.* [X2] teach that the support has significant effect on the activity of the immobilized enzyme, which would affect the yield. Sabbani *et al.* [U3] also teach that the chemical nature of the support has a significant influence on catalytic activity and enantioselectivity as well as the size of the particles of the support. These references are cited to demonstrate that the claimed method is not commensurate in scope as there is unpredictability in the art of enzyme catalysis with regard to the chemical identity and size of the support of an immobilized enzyme and with regard to

the shape of the activity curve of each specific lipase versus the water concentration in organic solvents. Applicant's arguments and claims are not commensurate in scope with the showing for at least the reasons above and therefore, do not overcome the rejection.

Conclusion

Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). It is applicants' burden to indicate how amendments are supported by the ORIGINAL disclosure. Due to the procedure outlined in MPEP 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 USC 102 or 35 USC 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone

number is (571) 272-0922. The examiner can normally be reached on Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, M. Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sandra Saucier/
Primary Examiner
Art Unit 1651